US011944733B2

(12) **United States Patent**
Pudil et al.

(10) **Patent No.: US 11,944,733 B2**
(45) **Date of Patent: Apr. 2, 2024**

(54) **SODIUM AND BICARBONATE CONTROL**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **17/529,809**

(22) Filed: **Nov. 18, 2021**

(65) **Prior Publication Data**

US 2023/0149607 A1 May 18, 2023

(51) **Int. Cl.**
A61M 1/16 (2006.01)

(52) **U.S. Cl.**
CPC ***A61M 1/1696*** (2013.01); ***A61M 1/1607*** (2014.02); ***A61M 1/1658*** (2013.01); *A61M 2205/3324* (2013.01)

(58) **Field of Classification Search**
CPC A61M 1/1607; A61M 1/1658; A61M 1/1696; A61M 2205/3324; A61M 2205/50; A61M 2230/208; A61M 1/1609; A61M 2205/3317; A61M 1/1656; A61M 1/287; A61M 1/1666; A61M 1/169; A61M 1/1566; A61M 1/36224
See application file for complete search history.

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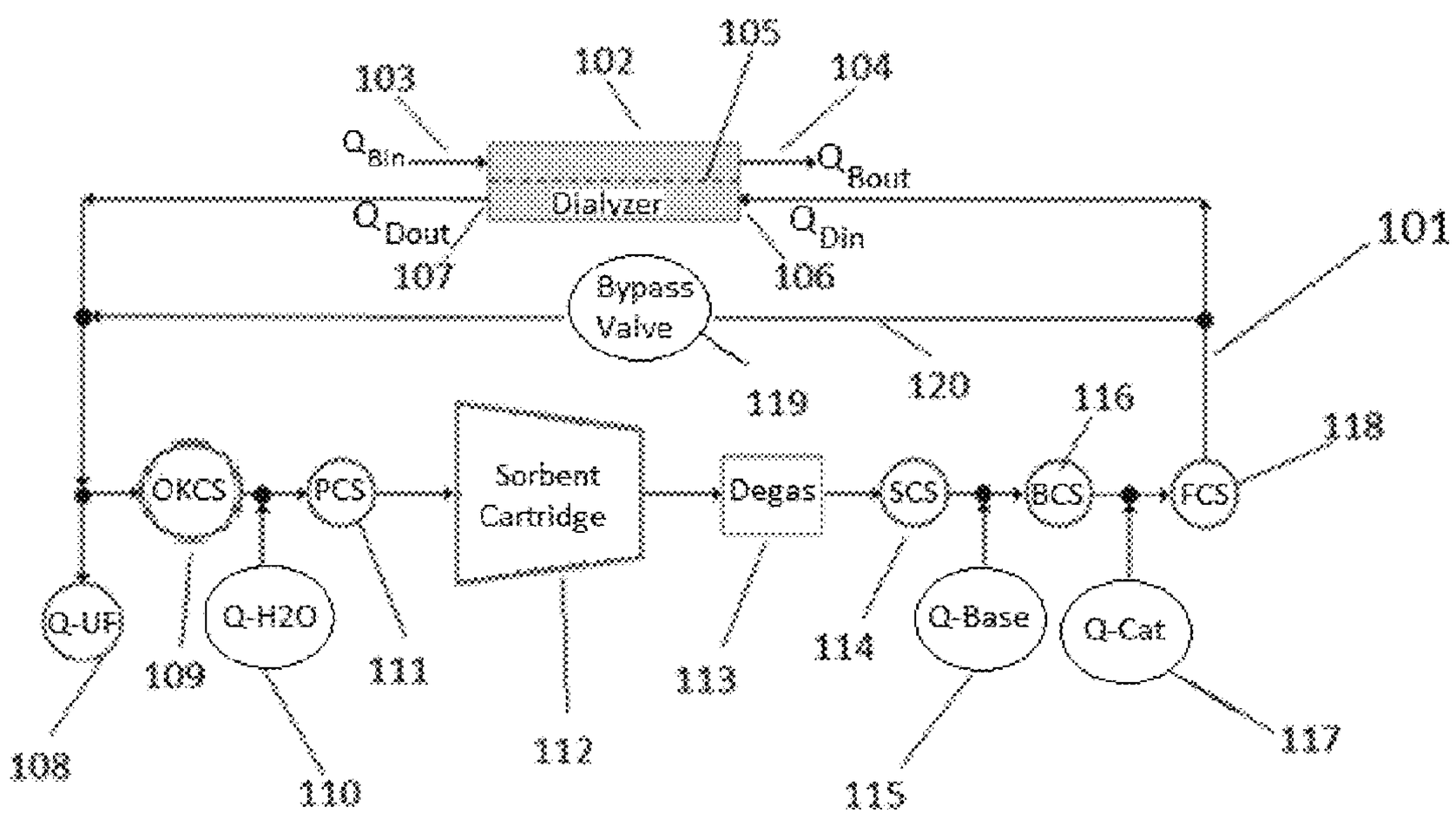
Primary Examiner — Pranav N Patel

(57) **ABSTRACT**

The disclosure relates to systems and methods for controlling the sodium and bicarbonate concentrations in a dialysate. The systems and methods can use conductivity sensors to control the addition of water and bicarbonate to accurately control the final concentrations of both sodium and bicarbonate.

18 Claims, 8 Drawing Sheets



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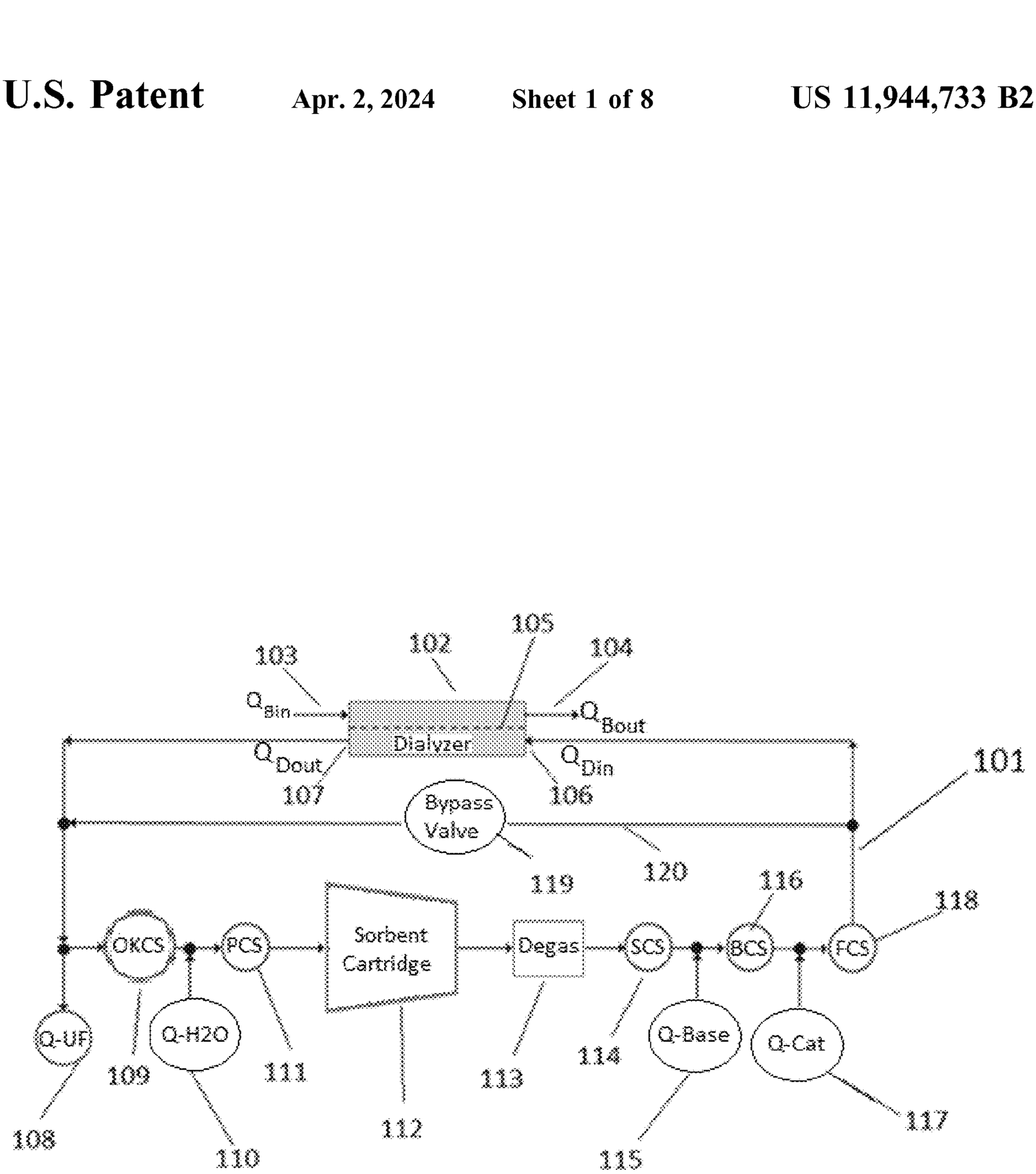
103
102
105
104
Q_{Bin}
Q_{Bout}
Dialyzer
Q_{Dout}
Q_{Din}
107
106
101
Bypass Valve
119
120
116
118
OKCS
PCS
Sorbent Cartridge
Degas
SCS
BCS
FCS
Q-UF
Q-H2O
Q-Base
Q-Cat
109
111
113
114
108
110
112
115
117

FIG. 1

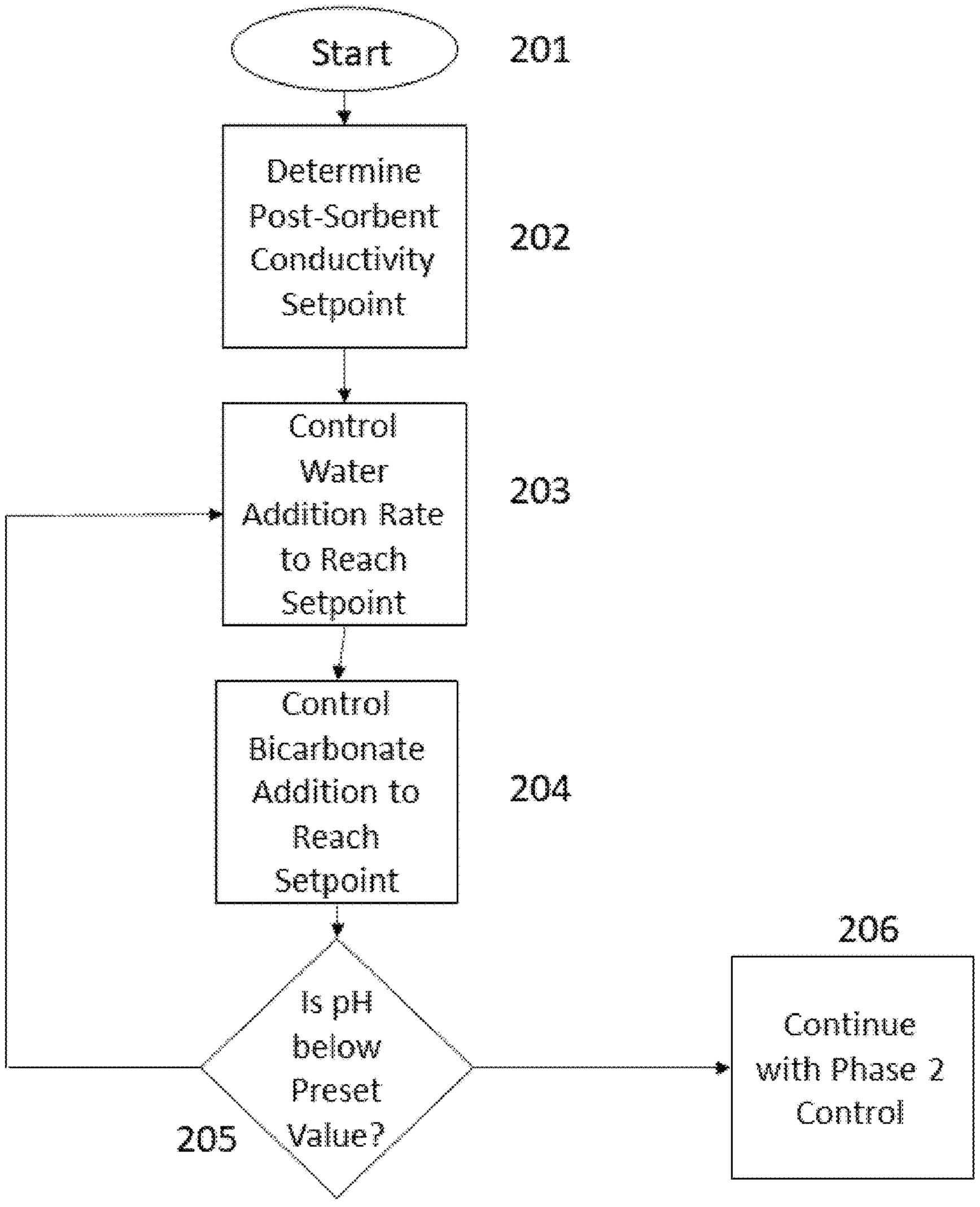
Start
201
Determine Post-Sorbent Conductivity Setpoint
202
Control Water Addition Rate to Reach Setpoint
203
Control Bicarbonate Addition to Reach Setpoint
204
Is pH below Preset Value?
205
Yes
206
Continue with Phase 2 Control

FIG. 2

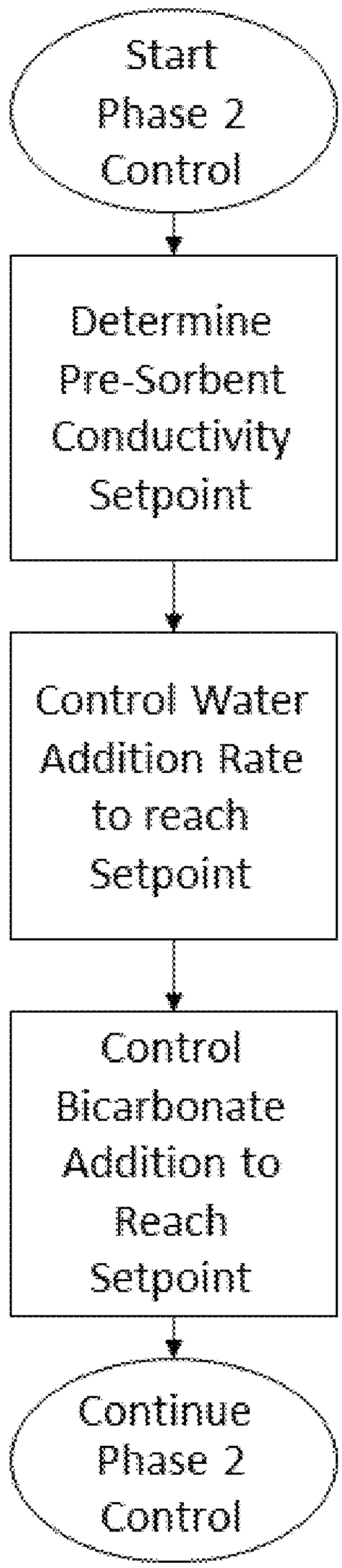
Start Phase 2 Control
301
Determine Pre-Sorbent Conductivity Setpoint
302
Control Water Addition Rate to reach Setpoint
303
Control Bicarbonate Addition to Reach Setpoint
304
Continue Phase 2 Control
305

FIG. 3

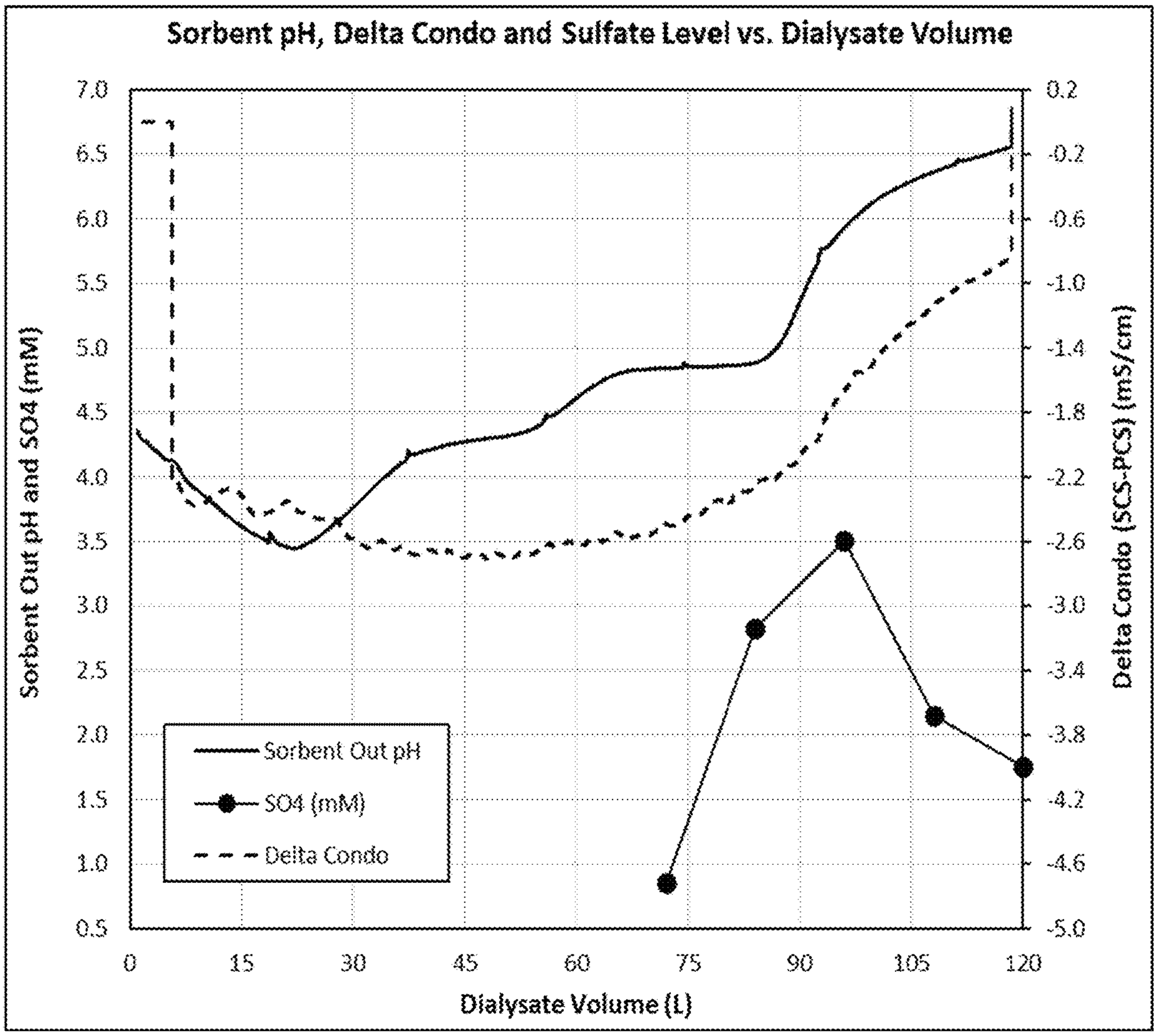
Sorbent pH, Delta Condo and Sulfate Level vs. Dialysate Volume
Sorbent Out pH and SO4 (mM)
Delta Condo (SCS-PCS) (mS/cm)
Dialysate Volume (L)
Sorbent Out pH
SO4 (mM)
Delta Condo
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.2
-0.2
-0.6
-1.0
-1.4
-1.8
-2.2
-2.6
-3.0
-3.4
-3.8
-4.2
-4.6
-5.0
0
15
30
45
60
75
90
105
120

FIG. 4

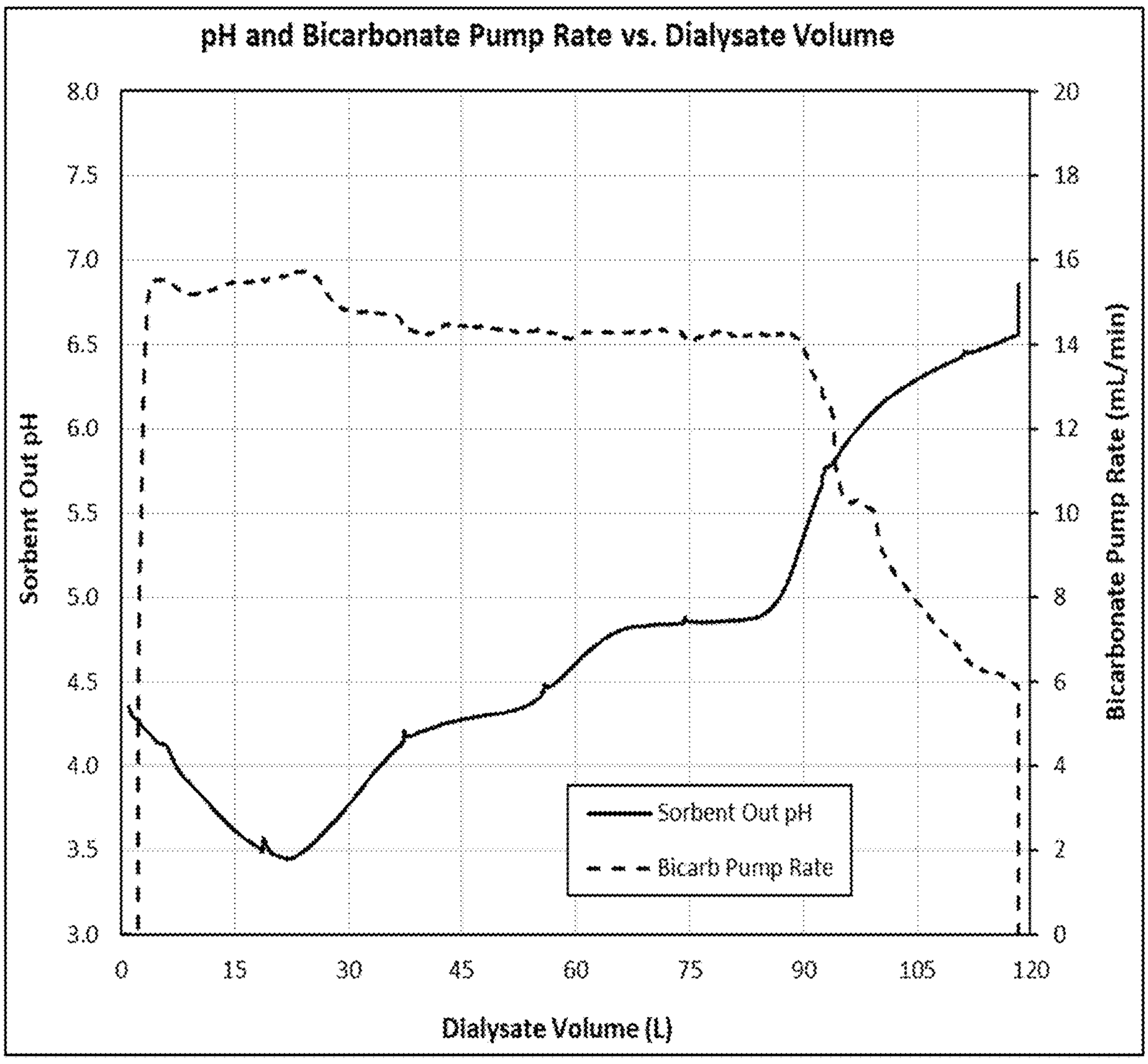
pH and Bicarbonate Pump Rate vs. Dialysate Volume
Sorbent Out pH
Bicarbonate Pump Rate (mL/min)
Dialysate Volume (L)
Sorbent Out pH
Bicarb Pump Rate
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
20
18
16
14
12
10
8
6
4
2
0
0
15
30
45
60
75
90
105
120

FIG. 5

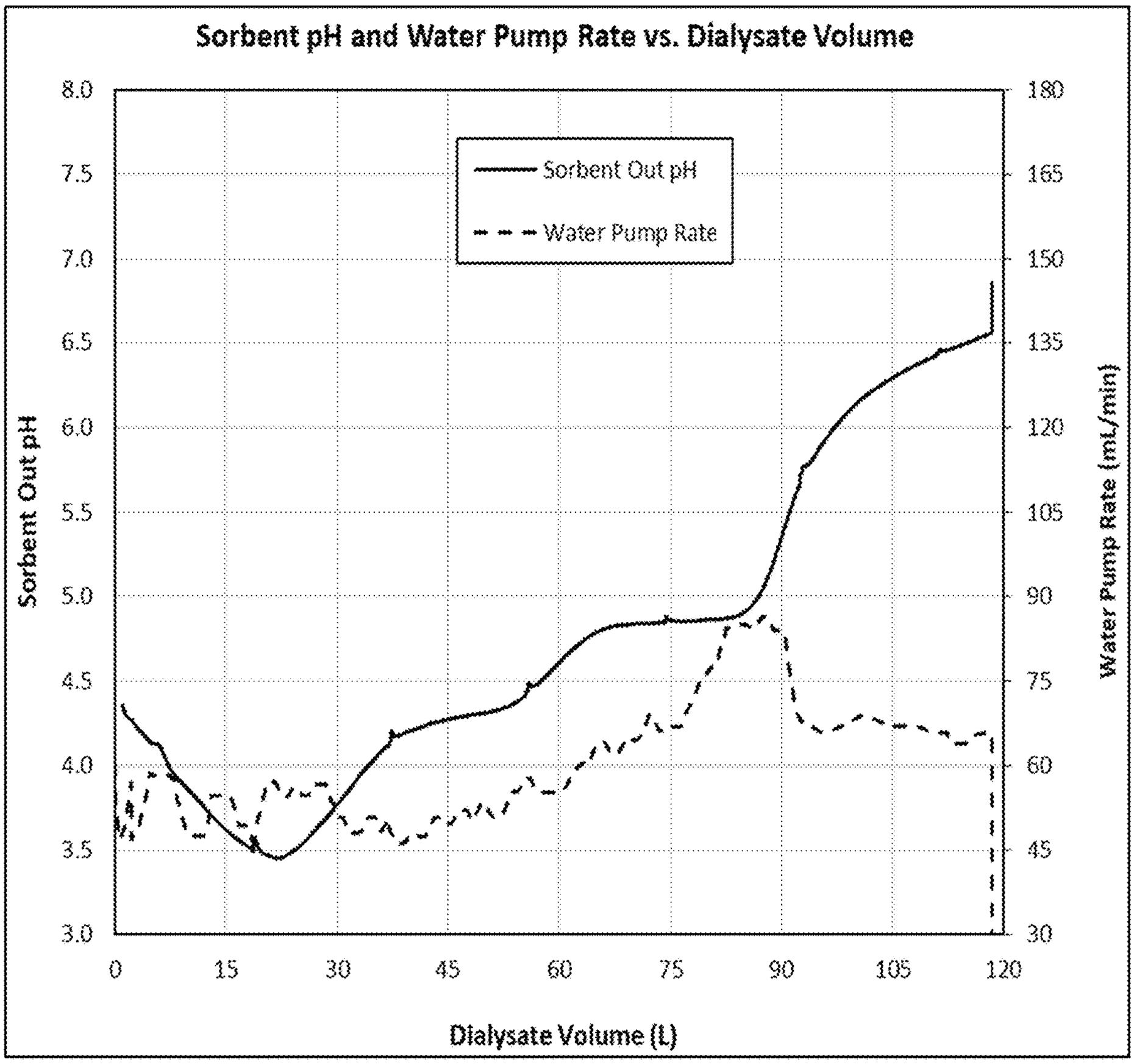
Sorbent pH and Water Pump Rate vs. Dialysate Volume
Sorbent Out pH
Water Pump Rate
Sorbent Out pH
Water Pump Rate (mL/min)
Dialysate Volume (L)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
180
165
150
135
120
105
90
75
60
45
30
0
15
30
45
60
75
90
105
120

FIG. 6

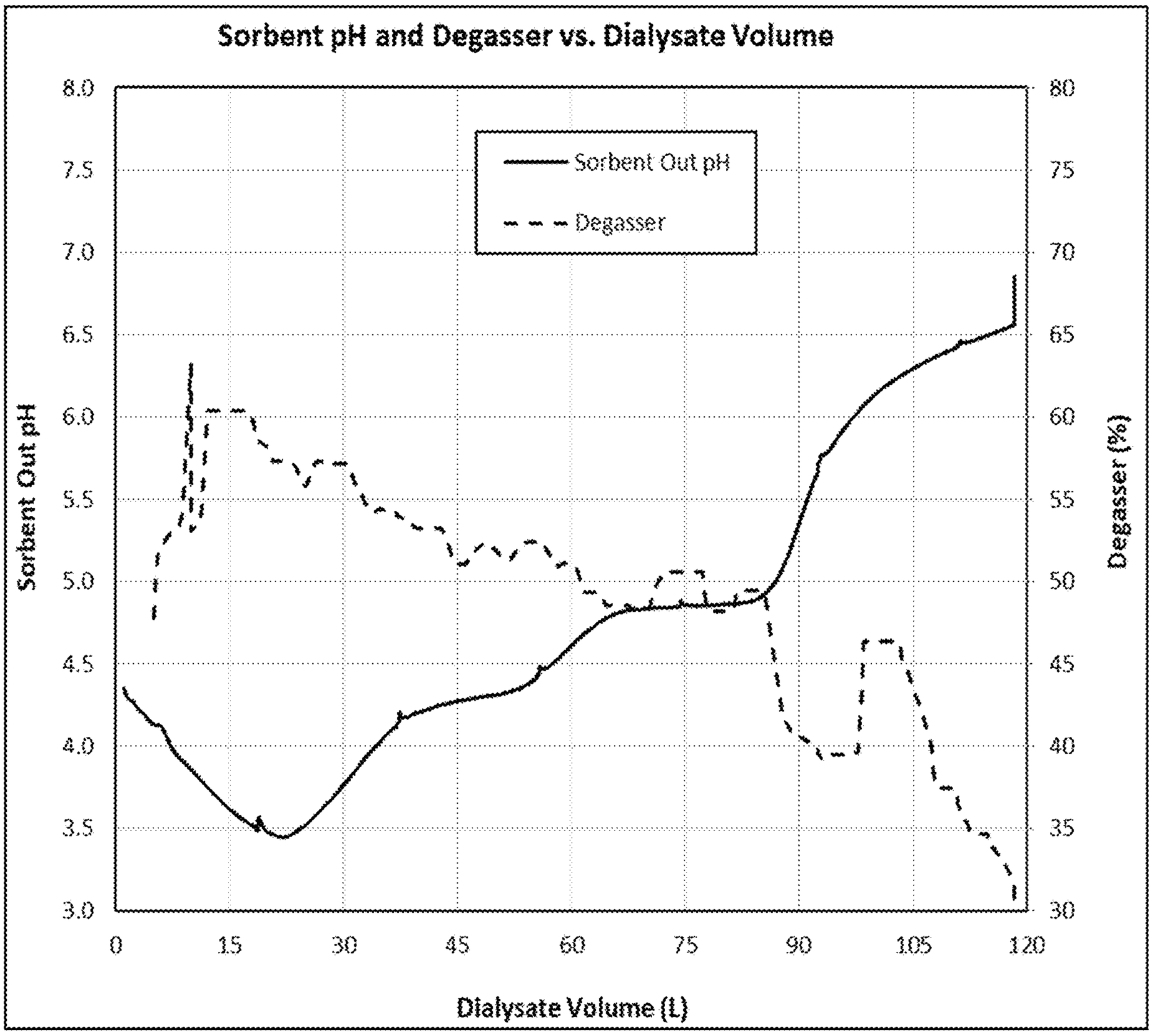
Sorbent pH and Degasser vs. Dialysate Volume
Sorbent Out pH
Degasser
Sorbent Out pH
Degasser (%)
Dialysate Volume (L)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
80
75
70
65
60
55
50
45
40
35
30
0
15
30
45
60
75
90
105
120

FIG. 7

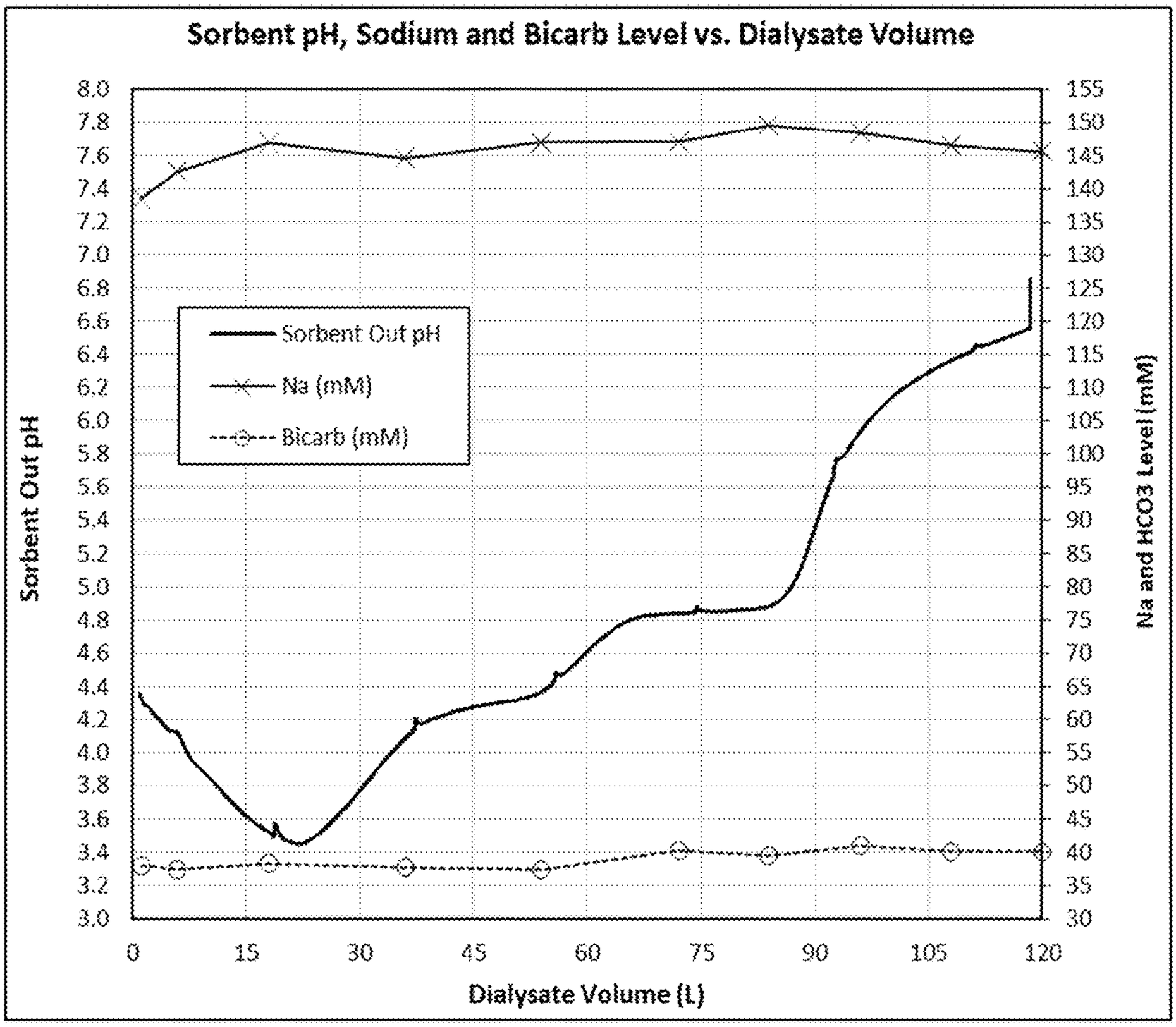
Sorbent pH, Sodium and Bicarb Level vs. Dialysate Volume
Sorbent Out pH
Na and HCO3 Level (mM)
Dialysate Volume (L)
Sorbent Out pH
Na (mM)
Bicarb (mM)
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
3.2
3.0
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
0
15
30
45
60
75
90
105
120

FIG. 8

SODIUM AND BICARBONATE CONTROL

FIELD

Systems, components, and methods are provided for controlling the sodium and bicarbonate concentrations in a dialysate. The systems, components, and methods can use conductivity sensors to control the addition of water and bicarbonate to accurately control the final concentrations of both sodium and bicarbonate.

BACKGROUND

Sorbent-based recirculating dialysis systems often remove urea from spent dialysate by first converting the urea to carbon dioxide and ammonium ions, and then removing the ammonium ions from solution. The formation of carbon dioxide, which exists in equilibrium with bicarbonate, makes control over the bicarbonate concentration of the dialysate difficult. In a typical regenerative dialysis sorbent system sodium and bicarbonate are partially removed or generated across a sorbent cartridge, usually to unpredictable levels. Therefore, the amount of sodium and bicarbonate to add to the dialysate to achieve a desired prescription level is unpredictable and can lead to inaccurate levels.

Hence, there is a need for systems and methods for controlling the bicarbonate and sodium concentrations in the dialysate of a sorbent-based dialysis system. The need extends to systems and methods that allow for accurate control of sodium and bicarbonate without the need to directly measure and adjust the bicarbonate concentration prior to the dialysate reaching the dialyzer. There is a further need for systems and methods that can control the bicarbonate and sodium concentration throughout an entire dialysis session, even as the pH and composition of the solution leaving the sorbent cartridge changes.

SUMMARY OF THE INVENTION

The problem to be solved is controlling bicarbonate and sodium concentration in a dialysate throughout a dialysis session. The solution is to use a two-phase control, removing substantially all of the bicarbonate from solution during a first low pH phase, and then using information obtained during the first phase to control the bicarbonate and sodium concentration in a second, higher pH phase.

The first aspect relates to a system. In any embodiment, the system can include a dialysate flow path; the dialysate flow path fluidly connectable to a dialysate inlet of a dialyzer and a dialysate outlet of the dialyzer; a sorbent cartridge in the dialysate flow path; a degasser in the dialysate flow path downstream of the sorbent cartridge; a bicarbonate source fluidly connected to the dialysate flow path; a water source fluidly connected to the dialysate flow path; a first conductivity sensor downstream of the sorbent cartridge; and a control system; the control system programmed to determine a pH of a fluid exiting the sorbent cartridge; wherein: while pH of the fluid exiting the sorbent cartridge is below a preset pH, the control system is programmed to control a sodium concentration in the fluid based on a sodium prescription and a conductivity measured by the first conductivity sensor; and to control a bicarbonate concentration in the fluid based on a bicarbonate prescription.

In any embodiment, the preset pH can be about 4.8.

In any embodiment, the sorbent cartridge can include zirconium phosphate at a low pH.

In any embodiment, while the pH of the fluid exiting the sorbent cartridge is below the preset pH, the control system can be programmed to control the sodium concentration in the fluid by adding water from a water source upstream of the sorbent cartridge to a target post-sorbent conductivity setpoint.

In any embodiment, while the pH of the fluid exiting the sorbent cartridge is below the preset pH, the control system can be programmed to control the bicarbonate concentration in the fluid by adding bicarbonate from a bicarbonate source downstream of the sorbent cartridge to a target conductivity delta between a conductivity sensor after the sorbent cartridge and a conductivity sensor after the bicarbonate source.

In any embodiment, the system can include a hydrochloric acid source fluidly connected to the dialysate flow path upstream of the sorbent cartridge.

In any embodiment, the system can include at least one infusate source downstream of the sorbent cartridge.

In any embodiment, the control system can be programmed to detect release of sulfate ions from the sorbent cartridge.

In any embodiment, wherein the control system can be programmed to dilute the fluid during the release of sulfate ions.

In any embodiment, while the pH of the fluid exiting the sorbent cartridge is above a preset pH, the control system can be programmed to control the sodium concentration in the fluid by adding water from a water source upstream of the sorbent cartridge to a target pre-sorbent conductivity setpoint.

In any embodiment, the pre-sorbent conductivity can be measured with a second conductivity sensor upstream of the sorbent cartridge.

In any embodiment, the target pre-sorbent conductivity setpoint can be a conductivity measured upstream of the sorbent cartridge while the pH is below the preset pH.

In any embodiment, while the pH of the fluid exiting the sorbent cartridge is above a preset pH, the control system can be programmed to control the bicarbonate concentration in the fluid by adding bicarbonate to reach a target post-bicarbonate conductivity setpoint.

In any embodiment, the target post-bicarbonate conductivity setpoint can be based on the sodium and a bicarbonate prescription.

In any embodiment, the pH of the fluid exiting the sorbent cartridge can be measured with a pH sensor downstream of the sorbent cartridge.

In any embodiment, the pH of the fluid exiting the sorbent cartridge can be measured based on changes to a degasser output.

In any embodiment, the pH of the fluid exiting the sorbent cartridge can be measured based on a conductivity change across the sorbent cartridge measured by the first conductivity sensor and a second conductivity sensor upstream of the sorbent cartridge.

In any embodiment, the pH of the fluid exiting the sorbent cartridge can be measured based on a volume of the water added from the water source.

In any embodiment, the control system can be programmed to isolate the sorbent cartridge prior to determining the pH of the fluid exiting the sorbent cartridge.

The features disclosed as being part of the first aspect can be in the first aspect, either alone or in combination, or follow any arrangement or permutation of any one or more of the described elements. Similarly, any features disclosed as being part of the first aspect can be in a second aspect

described below, either alone or in combination, or follow any arrangement or permutation of any one or more of the described elements.

The second aspect relates to a method. In any embodiment, the method can include determining a pH of a fluid exiting a sorbent cartridge of a sorbent dialysis system; and while pH of the fluid exiting the sorbent cartridge is below a preset pH, controlling a sodium concentration in the fluid based on a sodium prescription and a conductivity measured by a first conductivity sensor downstream of the sorbent cartridge; and controlling a bicarbonate concentration in the fluid based on a bicarbonate prescription.

In any embodiment, the preset pH can be about 4.8.

In any embodiment, the sorbent cartridge can include zirconium phosphate at a low pH.

In any embodiment, while the pH of the fluid exiting the sorbent cartridge is below a preset pH, the step of controlling the sodium concentration in the fluid can include adding water from a water source upstream of the sorbent cartridge to a target post-sorbent conductivity setpoint.

In any embodiment, while the pH of the fluid exiting the sorbent cartridge is below a preset pH, the step of controlling the bicarbonate concentration in the fluid can include adding bicarbonate from a bicarbonate source upstream of the sorbent cartridge and degasser to a target post-bicarbonate conductivity setpoint.

In any embodiment, the post-bicarbonate conductivity set point can be based on a conductivity increase between fluid downstream of the degasser and upstream of the bicarbonate source and fluid downstream of the bicarbonate source.

In any embodiment, the method can include the step of adding hydrochloric acid to the dialysate flow path upstream of the sorbent cartridge.

In any embodiment, while the pH of the fluid exiting the sorbent cartridge is above a preset pH, the method can include controlling the sodium concentration in the fluid by adding water from a water source upstream of the sorbent cartridge to a target pre-sorbent conductivity setpoint.

In any embodiment, target pre-sorbent conductivity setpoint can be a pre-sorbent conductivity measured while the pH is below the preset pH.

In any embodiment, while the pH of the fluid exiting the sorbent cartridge is above a preset pH, the step of controlling the bicarbonate concentration in the fluid can include adding bicarbonate to reach a post-bicarbonate conductivity setpoint.

In any embodiment, the post-bicarbonate conductivity setpoint can be based on the sodium and a bicarbonate prescription.

The features disclosed as being part of the second aspect can be in the second aspect, either alone or in combination, or follow any arrangement or permutation of any one or more of the described elements. Similarly, any features disclosed as being part of the second aspect can be in the first aspect, either alone or in combination, or follow any arrangement or permutation of any one or more of the described elements.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a simplified drawing of a dialysis system.

FIG. **2** is a flow chart showing a method of controlling sodium and bicarbonate during a low-pH phase.

FIG. **3** is a flow chart showing a method of controlling sodium and bicarbonate during a high-pH phase.

FIG. **4** is a graph showing sorbent pH, conductivity changes, and sulfate level vs. dialysate volume for a simulated dialysis session.

FIG. **5** is a graph showing sorbent outlet pH and bicarbonate pump rate vs. dialysate volume for a simulated dialysis session.

FIG. **6** is a graph showing sorbent outlet pH and water pump rate vs. dialysate volume for a simulated dialysis session.

FIG. **7** is a graph showing sorbent outlet pH and degasser pump output vs. dialysate volume for a simulated dialysis session.

FIG. **8** is a graph showing sorbent outlet pH, dialysate sodium level, and dialysate bicarbonate level vs. dialysate volume for a simulated dialysis session

DETAILED DESCRIPTION

Unless defined otherwise, all technical and scientific terms used have the same meaning as commonly understood by one of ordinary skill in the art.

The articles "a" and "an" are used to refer to one to over one (i.e., to at least one) of the grammatical object of the article. For example, "an element" means one element or over one element.

The term "adding," to "add," or "addition" refers to pumping additional fluid into an existing fluid or into a component or system.

The term "bicarbonate" refers to $HCO3^-$ ions, as well as any species existing in equilibrium with bicarbonate ions, including carbonate ions and carbon dioxide.

The term "bicarbonate concentration" refers to an amount of bicarbonate dissolved in a solvent per a given amount of solvent.

A "bicarbonate prescription" is an intended bicarbonate concentration in the dialysate or blood.

The term "bicarbonate source" can refer to a source of bicarbonate ions or bicarbonate predecessors. The bicarbonate can be in acid or basic form, and can include substances that react to form bicarbonate when used in a dialysis system.

The term "blood flow rate" refers to a volume of blood moving through a system per unit of time.

The term "comprising" includes, but is not limited to, whatever follows the word "comprising." Use of the term indicates the listed elements are required or mandatory but that other elements are optional and may be present.

The term "conductivity" refers to the inverse of the electrical resistance of a fluid.

The term "conductivity change across the sorbent cartridge" refers to a difference in conductivity of a fluid prior to the fluid entering a sorbent cartridge and after the fluid exits the sorbent cartridge.

The term "conductivity increase" refers to a positive change in conductivity of a fluid as the fluid moves through a system.

The term "conductivity sensor" refers to any component capable of measuring the electrical conductance or the electrical resistance of a fluid.

The term "consisting of" includes and is limited to whatever follows the phrase "consisting of." The phrase indicates the limited elements are required or mandatory and that no other elements may be present.

The term "consisting essentially of" includes whatever follows the term "consisting essentially of" and additional

elements, structures, acts, or features that do not affect the basic operation of the apparatus, structure or method described.

The terms "control," "controlling," or "controls" can refer to the ability of one component to direct the actions of a second component.

A "control system" is a device which monitors and affects the operational conditions of a given system. The operational conditions are typically referred to as output variables of the system wherein the output variables can be affected by adjusting certain input variables.

A "degasser" refers to any device, component, or system that can be used to remove one or more gases from a fluid.

The term "degasser output" can refer to an amount of gas removed from a fluid by a degasser, or to the composition of gases removed from the fluid.

The term "detect" refers to ascertaining a state of a system or component.

The terms "determining," "determines," and the like, generally refer to, in the broadest reasonable interpretation, any process or method for obtaining or coming to a decision, value, number, or finding, for any one or more value, output, parameter, or variable, by any means applicable to the relevant parameter being determined.

The term "dialysate" refers to any mixture that provides for passing solutes of any type through a membrane of any type. Typically, a dialysate contains a concentration of solutes to exchange solutes across a gradient to and from the dialysate during dialysis therapy.

The term "dialysate flow path" refers to a pathway through which dialysate travels during dialysis therapy.

The term "dialysate flow rate" refers to a volume of dialysate moving through a system per unit of time.

The term "dialysate inlet" refers to an opening or conduit through which dialysate can enter a component.

The term "dialysate outlet" refers to an opening or conduit through which dialysate can exit a component.

The term "dialyzer" can refer to a cartridge or container with two flow paths separated by semi-permeable membranes. One flow path can be for blood and one flow path can be for dialysate. The membranes can be in hollow fibers, flat sheets, or spiral wound or other conventional forms known to those of skill in the art. Membranes can be selected from any one or combination of materials: polysulfone, polyethersulfone, poly (methyl methacrylate), modified cellulose, or other materials known to those skilled in the art.

The term "dialyzer size" refers to the amount of fluid that can be contained within a dialyzer.

The term "dilute" means to lower a concentration of one or more solutes in solution.

The term "downstream" refers to a position of a first component in a flow path relative to a second component wherein fluid, gas, or combinations thereof, will pass by the second component prior to the first component during normal operation. The first component can be said to be "downstream" of the second component, while the second component is "upstream" of the first component.

The term "estimate" can refer to an approximation of a value for a particular parameter.

The terms "exit" or "exiting" refer to a fluid leaving a container or component.

The term "fluidly connectable" refers to the ability to provide passage of fluid, gas, or combinations thereof, from one point to another point. The ability to provide such passage can be any mechanical connection, fastening, or forming between two points to permit the flow of fluid, gas, or combinations thereof. The two points can be within or between any one or more of compartments, modules, systems, components, and rechargers, all of any type. Notably, the components that are fluidly connectable, need not be a part of a structure. For example, an outlet "fluidly connectable" to a pump does not require the pump, but merely that the outlet has the features necessary for fluid connection to the pump.

The term "fluidly connected" refers to a particular state or configuration of one or more components such that fluid, gas, or combination thereof, can flow from one point to another point. The connection state can also include an optional unconnected state or configuration, such that the two points are disconnected from each other to discontinue flow. It will be further understood that the two "fluidly connectable" points, as defined above, can form a "fluidly connected" state. The two points can be within or between any one or more of compartments, modules, systems, components, all of any type.

The term "hydrochloric acid source" refers to any source from which hydrochloric acid, or HCl, can be obtained.

The term "infusate source" refers to one or more sources of cations, such as potassium, calcium, or magnesium cations, for addition to a dialysate.

The term "isolate" refers to configuring a system such that a given component is not in fluid communication with a second given component.

The term "low pH" refers to a pH low enough that will result in substantially all bicarbonate being converted to carbon dioxide.

The term "measuring" or "to measure" can refer to determining any parameter or variable. The parameter or variable can relate to any state or value of a system, component, fluid, gas, or mixtures of one or more gases or fluids.

The term "patient bicarbonate level" refers to the bicarbonate concentration in the blood of a patient.

The term "patient size" refers to the mass or weight of a patient.

The term "patient urea level" refers to the urea concentration in the blood of a patient.

"pH" is a value equal to the negative log of the H^+ ion concentration in a fluid.

The term "pH sensor" refers to any sensor or set of sensors that can be used to determine the pH of a fluid.

The term "preset" refers to a value of a parameter or state of a component or system that is determined in advance of a dialysis session.

The term "programmed," when referring to a processor, can mean a series of instructions that cause a processor to perform certain steps.

The term "release" refers to one or more substances being added by a component to a fluid.

The term "sodium" refers to Na ions in solution.

The term "sodium concentration" refers to an amount of sodium ions dissolved in a given amount of solvent.

A "sodium prescription" is an intended sodium concentration in a dialysate or blood.

The terms "sorbent cartridge" and "sorbent container" can refer to a cartridge containing one or more sorbent materials for removing specific solutes from solution, such as urea. The term "sorbent cartridge" does not require the contents in the cartridge be sorbent based, and the contents of the sorbent cartridge can be any contents that can remove waste products from a dialysate. The sorbent cartridge may include any suitable amount of one or more sorbent materials. In certain instances, the term "sorbent cartridge" can refer to a cartridge which includes one or more sorbent materials in

addition to one or more other materials capable of removing waste products from dialysate. "Sorbent cartridge" can include configurations where at least some materials in the cartridge do not act by mechanisms of adsorption or absorption. In any embodiment, a system may include a number of separate cartridges which can be physically separated or interconnected wherein such cartridges can be optionally detached and reattached as desired. The term "sulfate ions" refers to SO_4^{2-} in acid or basic form, or with any counter ions.

The term "target post-bicarbonate conductivity setpoint" refers to a conductivity value, measured after bicarbonate has been added to a fluid, that will result in an intended prescription for a dialysate.

The term "target post-sorbent conductivity setpoint" refers to a conductivity value, measured after a fluid has passed through a sorbent cartridge, that will result in an intended prescription for a dialysate.

The term "target pre-sorbent conductivity setpoint" refers to a conductivity value, measured before a fluid has passed through a sorbent cartridge, that will result in an intended prescription for a dialysate.

The term "ultrafiltration rate" refers to a volume of fluid removed from the blood of a patient per unit of time.

The term "upstream" refers to a position of a first component in a flow path relative to a second component wherein fluid, gas, or combinations thereof, will pass by the first component prior to the second component during normal operation. The first component can be said to be "upstream" of the second component, while the second component is "downstream" of the first component.

A "water source" can be any fluid source from which water can be obtained. The source can be any type of reservoir, fluid line, or receptacle. The water from the water source can be water with or without any dissolved solutes, including one or more buffer or ions.

"Zirconium phosphate" is a sorbent material that removes cations from a fluid, exchanging the removed cations for different cations.

Sodium and Bicarbonate Control

FIG. **1** is a simplified diagram of a sorbent-based dialysis system. A dialyzer **102** can be fluidly connected to an extracorporeal flow path (not shown) and fluidly connectable to a dialysate flow path **101**. Blood from a patient can enter the dialyzer **102** through blood inlet **103** and exit the dialyzer **102** through blood outlet **104**. At the same time, dialysate can enter the dialyzer **102** through dialysate inlet **106** and exit through dialysate outlet **107**. The dialysate and blood are separated in the dialyzer **102** by semi-permeable membrane **105**. Solutes and fluid can pass between the blood and the dialysate through semi-permeable membrane **105**.

After exiting the dialyzer **102**, the dialysate can be pumped through dialysate flow path **101**. One or more pumps (not shown) can provide the driving force necessary to control the movement of dialysate through the dialysate flow path **101**. A portion of the dialysate can be drawn off as ultrafiltrate by ultrafiltration system **108**. If necessary to control sodium concentration, water can be added to the dialysate from water source **110**. The used dialysate can be pumped through sorbent cartridge **112** to regenerate the dialysate.

The sorbent cartridge **112** can include one or more sorbent materials to remove solutes from the dialysate, allowing the dialysate to be reused. In certain embodiments, the sorbent cartridge **112** can include activated carbon to remove creatinine, glucose, uric acid, β2-microglobulin and other non-ionic toxins, except urea, from the dialysate. The sorbent cartridge can also include urease, which converts urea to ammonium ions and carbon dioxide. Zirconium oxide in the sorbent cartridge **112** can remove phosphate, fluoride, and other anions from the dialysate. Zirconium phosphate in sorbent cartridge **112** can remove the ammonium ions generated from the breakdown of urea by the urease, as well as potassium, calcium, and magnesium cations. The cations removed by the zirconium phosphate can be exchanged for sodium and hydrogen ions.

Carbon dioxide present in the dialysate exiting the sorbent cartridge **112** can be removed by degasser **113** located downstream of the sorbent cartridge **112**. Bicarbonate can be added to the dialysate from bicarbonate source **115** and cations, such as potassium, magnesium, and calcium, can be added back into the dialysate from cation infusate source **117**. In certain embodiments, bypass line **120** and bypass valve **119** can be included to bypass either the dialyzer **102** or the sorbent cartridge **112**.

One of skill in the art will understand that the system illustrated in FIG. **1** is a simplified system for illustrative purposes only. Additional components can be included. For example, additional pumps and valves can be included for operation of the degassing system, as well as control over ultrafiltration and addition of water, bicarbonate, and cation infusate. The pumps and valves can be operated by a control system (not shown). The control system can be programmed to receive data from sensors at various positions in the dialysate flow path **101**, to determine any parameters or system state based on the received data, and to control the components of the dialysis system. For example, conductivity sensor **109** can be included to determine the conductivity of the dialysate exiting the dialyzer **102**. Conductivity sensor **111** can be included to determine the conductivity of dialysate after addition of water and prior to reaching the sorbent cartridge **112**. Conductivity sensor **114** can be included to measure the conductivity of the dialysate after the degasser and prior to addition of bicarbonate solution. Conductivity sensor **116** can be used to measure the conductivity of the dialysate after addition of bicarbonate and prior to addition of cation infusate. Conductivity sensor **118** can be included to measure the conductivity after the addition of the cation infusate to ensure the final dialysate has a proper composition prior to reaching the dialyzer **102**. Additional sensors (not shown), such as temperature sensors, pressure sensors, pH sensors, or any other sensors can be included.

In certain embodiments, the system can control the sodium and bicarbonate concentrations in the dialysate using a two-phase approach. FIG. **2** is a flow chart showing control over the sodium and bicarbonate concentration during the first phase. In step **201**, the process can begin. In the beginning of a dialysis session, the sorbent cartridge **112** can be a low-pH sorbent cartridge. The pH of the sorbent cartridge can be controlled by controlling the initial hydrogen to sodium ratio of the zirconium phosphate. A higher proportion of hydrogen ions will result in a lower pH of fluid exiting the sorbent cartridge.

When the sorbent cartridge effluent pH is below a preset pH, substantially all bicarbonate in the dialysate will be converted to carbon dioxide and subsequently removed by the degasser, effectively reducing the total CO2 or bicarbonate to a level approaching 0-mM and allowing control over both the sodium and bicarbonate concentration in the dialysate. In step **202**, the system can determine a post-sorbent conductivity setpoint that will result in a desired

sodium concentration. Knowing that the bicarbonate level is near zero allows an accurate conductivity value to be determined because the sorbent effluent will mainly depend on the concentration of sodium and chloride. The post-sorbent conductivity setpoint can be set based on both the sodium and bicarbonate prescriptions. For example, if a dialysate sodium of 140-mM and bicarbonate of 40-mM are desired, the sodium chloride level needed at sorbent outlet would be 100-mM and the conductivity set-point would correspond to the conductivity of a 100-mM sodium chloride solution. The remaining 40 mM of sodium will be added by addition of sodium bicarbonate after the dialysate passes through the degasser **113**. Water from water source **110** can be added to the dialysate to dilute the dialysate if necessary to reach the post-sorbent conductivity setpoint in step **203**. Although illustrated in FIG. **1** as upstream of the sorbent cartridge **112**, the water source **110** can alternatively be positioned downstream of the sorbent cartridge **112**.

The bicarbonate concentration of the dialysate is controlled in step **204**. As described, during phase 1 control, the pH of the sorbent cartridge effluent is low enough to convert substantially all bicarbonate to carbon dioxide, which is removed by degasser **113**. To accurately control bicarbonate concentration in the dialysate, sodium bicarbonate from bicarbonate source **115** can be added. The system can control the addition of bicarbonate to achieve a post-bicarbonate conductivity setpoint as measured by conductivity sensor **116**. The post-bicarbonate conductivity setpoint can be a fixed value based on the sodium and bicarbonate prescription. Alternatively, the post-bicarbonate conductivity setpoint can be based on achieving a target conductivity delta between the post-degasser conductivity sensor **114** and the post-bicarbonate conductivity sensor **116**. For example, a bicarbonate prescription of 40-mM would require the addition of 40-mM bicarbonate from the bicarbonate source, which corresponds to a certain conductivity increase between conductivity sensor **114** and **116**. Therefore, the bicarbonate source can be added to achieve the desired conductivity increase at sensor **116** relative to sensor **114**. After the bicarbonate is added to the dialysate, a cation infusate can be added to control the potassium, calcium, and magnesium concentrations. In certain embodiments, the cation infusate can also include sodium. In such embodiments, the post-sorbent conductivity set point can be adjusted to account for the additional sodium.

As described, the phase 1 control over sodium and bicarbonate can continue while the sorbent effluent pH is low enough to convert substantially all the bicarbonate to carbon dioxide. In step **205**, the system can monitor the sorbent cartridge effluent pH, and determine whether the sorbent cartridge effluent pH is below a preset pH. If the sorbent cartridge effluent pH is below the preset pH, the method can continue in step **203**, with control over both sodium and bicarbonate. If the pH exceeds the preset pH, some level of bicarbonate can remain in the dialysate after passing through the sorbent cartridge **112** and degasser **113**. The system can then switch to a phase 2 control method in step **206**. In certain embodiments, the preset pH for the sorbent cartridge effluent pH can be about 4.8, which will result in substantially all the bicarbonate being removed from the dialysate.

One of skill in the art will understand that several options for determining when to switch to phase 2 control can be used. Optionally, the system can use a pH sensor at the outlet of the sorbent cartridge to measure the effluent pH. Alternatively, the system can monitor the degasser output to determine changes in the sorbent effluent pH. As the pH rises, there will be less CO_2 to degas, and the degasser output will decrease. In certain embodiments, the system can detect the sorbent cartridge effluent pH state based on conductivity changes across the sorbent cartridge. As the pH of the sorbent cartridge increases, the bicarbonate concentration, and corresponding sodium concentration, increases, resulting in a smaller conductivity change across the sorbent cartridge. The system can also detect the sorbent cartridge effluent pH state based on changes in the water addition rate needed to maintain the sorbent outlet conductivity target during phase one control. As the pH rises and the sodium bicarbonate concentration increases, the sorbent outlet conductivity will increase and require an increase in water dilution to maintain the post-sorbent conductivity setpoint. Periodic isolation of the sorbent cartridge from the dialyzer and measurement of the above parameters can also be used to predict the sorbent cartridge pH state. Isolation of the dialyzer removes unknown contributions to the dialysate from the patient and results on a more accurate prediction of the pH state. To isolate the sorbent cartridge from the dialyzer, dialysate can be pumped through a bypass line, such as bypass line **120** in FIG. **1**, recirculating the dialysate through the sorbent cartridge **112** without passing through the dialyzer **102**. Refinement of the pH state determination using the described methods can be achieved by using more than one method listed, either to refine detection with a single-method or used together. Also, detection can be refined based on early conductivity changes across the dialyzer and/or across the sorbent cartridge. These early conductivity changes can be indicative of patient levels and used to further refine detection of the dialysate pH. In addition, integration of the conductivity change across the sorbent cartridge can be used as a measure of the cumulative bicarbonate exposure to the sorbent cartridge, and transition to phase two control can be done when the cumulative exposure reaches a preset value.

Alternatively, the detection of sorbent outlet pH can be determined based on the conductivity change across the sorbent cartridge normalized to the water dilution rate needed to achieve the target post-sorbent conductivity setpoint by using equation (1): $(SCS-PCS)/(1-Q\text{-}H_2O/Q_{Dout})$, wherein SCS is the conductivity measured by conductivity sensor **114**, PCS is the conductivity measured by conductivity sensor, $Q\text{-}H_2O$ is the water addition rate from water source **110**, and Q_{Dout} is the dialysate flow rate at the dialyzer outlet **107**. In addition, the SCS and PCS values used in equation (1) can be offset in time due to the volume of the sorbent cartridge and the time it takes fluid to flow from the inlet of the cartridge to the outlet. For example, a sorbent cartridge with a void volume of 4 liters will require 8 minutes for fluid to flow from the inlet to outlet at a flow rate of 500-mL/min. Therefore, the SCS value at 8 minutes should be compared to the PCS value at 0 minutes. The conductivity delta across the sorbent cartridge, SCS-PCS, is mainly influenced by the concentration of sodium bicarbonate entering the sorbent cartridge, which is determined by the prescription and patient parameters. In the low pH phase, all of the sodium bicarbonate entering the cartridge is removed resulting in a conductivity decrease. Because the SCS-PCS, or conductivity delta across the sorbent cartridge, can vary in the low pH phase due to difference in prescription or patient parameters, a plateau value can be calculated and subsequent conductivity deltas across the sorbent cartridge can be compared to the plateau value to determine when the pH has increased to the preset value. The plateau value can be determined by averaging the SCS-PCS values over a certain time, or dialysate volume, and starting at a particular dialysate volume. For example, after 40-liters of

dialysate volume the SCS-PCS values, or the values calculated in Eq (1), can be averaged from to 50-liters. Then the conductivity delta across the sorbent cartridge (SCS-PCS) can be compared to the average plateau value to determine when the pH value has exceeded the preset value. For example, an increase in SCS-PCS of 0.44-mS/cm relative to the plateau value can indicate the pH has risen to a value exceeding 4.8. Values other than an increase of 0.44-mS/cm can be used depending on properties of the sorbent cartridge used or other factors such as dialysate prescription or patient parameters. The volume to start the averaging for the plateau value should start before the sorbent cartridge pH begins to rise. The volume can be based on the dialysate bicarbonate prescription. In a sorbent cartridge utilizing a zirconium phosphate sorbent as the pH controlling buffer source, the accumulation of bicarbonate through the sorbent cartridge will eventually exceed the buffering capacity of the zirconium phosphate and result in a rising pH. Therefore, a higher bicarbonate prescription will result in a sorbent cartridge pH rise sooner than a lower bicarbonate prescription. A bicarbonate prescription of 30-mM could start the plateau averaging at 60-liters and a bicarbonate prescription of 40-mM could start the plateau averaging at 40-liters, for example.

In certain embodiments, the sorbent cartridge effluent pH may remain below the preset pH value for the entire dialysis session. In such cases, the system can control the dialysate sodium and bicarbonate concentrations using the phase 1 method illustrated in FIG. **2** throughout the dialysis session. In certain embodiments, an acid source, such as a hydrochloric acid source, can be included upstream of the sorbent cartridge to acidify the dialysate prior to reaching the sorbent cartridge. Acidifying the dialysate can keep the sorbent cartridge effluent pH low, prolonging the time during which phase 1 control can be used. The low sorbent effluent pH can also be maintained by using a sufficient amount of zirconium phosphate at low pH, or by limiting the total volume of dialysate used during the dialysis session. In certain embodiments, the zirconium phosphate pH can refer to a slurry pH, which is the measured pH of zirconium phosphate slurried in water. A "low pH" zirconium phosphate can refer to zirconium phosphate having a slurry pH of below about 5.

As the pH rises above the preset pH, the amount of bicarbonate, post-degassing, can increase to greater than 1 mM, and potentially up to prescription levels of 30 to 40 mM, depending on the pH at sorbent outlet and the total CO_2 level in the spent dialysate entering the sorbent cartridge. During this second phase, the unpredictable bicarbonate level at sorbent outlet makes controlling to an accurate sodium and bicarbonate prescription level more difficult. FIG. **3** is a flow chart illustrating the phase 2 method of sodium and bicarbonate control in the dialysate with a higher pH in the dialysate exiting the sorbent cartridge. As described, the method can begin in step **301** using phase 2 control, after the sorbent cartridge effluent pH has exceeded the preset value.

In contrast to the phase 1 control illustrated in FIG. **2**, the phase 2 control of FIG. **3** can use a pre-sorbent conductivity set point. In step **302**, the system can determine the pre-sorbent conductivity set point as measured by conductivity sensor **111** illustrated in FIG. **1**. The pre-sorbent conductivity set point is based on learning the sorbent inlet conductivity value used towards the end of the first phase of control. Over the course of a therapy session, the patient blood and the dialysate will approach equilibrium with each other, and the dialysate outlet conductivity measured by conductivity sensor **109** and subsequent sorbent inlet conductivity measured by conductivity sensor **111** will reach a stable value. Therefore, if the first phase of control occurs over a significant volume, i.e., greater than 30-liters, the pre-sorbent conductivity value can be assumed to have reached a stable value and can be used as the pre-sorbent conductivity set point for the second phase of control. In addition, the rate of change in the pre-sorbent conductivity (PCS), or PCS profile, can be learned during the first phase of control and used to control to a PCS profile in the second phase of control. For example, a steadily changing PCS value can be fit to a curve or a line and the PCS values to target as a function of dialysate volume can be extrapolated based on the fit during phase 2. Using the pre-sorbent conductivity set point determined in step **302**, the system can control the water addition rate to achieve the pre-sorbent conductivity set point in step **303**.

The phase 2 control can also rely on a predictable change in chloride concentration across the sorbent cartridge. In the case of the REDY type sorbent system, the chloride concentration can be assumed to be unchanged across the sorbent cartridge. Therefore, the PCS value determined in phase 1 is equal to the PCS value needed to achieve the desired chloride level, based on the dialysate prescription, at the sorbent inlet and subsequently the sorbent outlet, relying on the unchanging chloride concentration across the sorbent cartridge. The second aspect of control during the second phase involves adding sodium bicarbonate post-sorbent cartridge at a rate Q-Base to a conductivity value (BCS), which is the conductivity measured by conductivity sensor **116**, based on the sodium and bicarbonate prescription value in step **304**. Because the composition of dialysate needed after addition of sodium bicarbonate is accurately known based on the prescription, the composition error is minimized using this approach. Depending on the sorbent outlet pH and the total CO_2 exiting the sorbent cartridge, the bicarbonate concentration can vary be between 1 mM and 40 mM in concentration. Typically, in phase 2 the sorbent outlet pH will increase steadily resulting in a gradual increase of the bicarbonate concentration exiting the sorbent cartridge. Therefore, the amount of sodium bicarbonate that must be added to achieve the post-bicarbonate conductivity setpoint may vary. In step **305**, the dialysis session can continue until the end of the session using the phase 2 control.

In certain embodiments, the system can use phase 1 control as long as possible before the sorbent cartridge effluent pH exceeds the preset value. Delaying the transition to phase 2 control as long as possible allows for further equilibration between the patient and dialysate and determination of a more accurate sorbent inlet conductivity setpoint or profile to be used during phase two control.

In some cases, there may be a need for an additional phase of control, between the first and second phases, due to release of sulfate from the sorbent cartridge. Some sorbent cartridge designs can remove sulfate when the sorbent cartridge is in a low pH phase, but as the pH rises (above 4.5 for example), the sulfate may be released. The release of sulfate will also result in the release of sodium, to maintain charge balance. At pH values above 3, sulfates primarily exist as a divalent anion and will require two sodium ions for charge balance. The release of sodium sulfate will result in a sorbent outlet conductivity increase that will require additional dilution water (Q-H2O) to maintain the sorbent outlet conductivity at the phase 1 set-point. However, because sulfate will be present in the sorbent outlet, an adjusted conductivity setpoint can be determined based on the methods used for phase one control, except with a non-zero level for sulfate, because although sulfate is being

released due to slightly higher sorbent outlet pH, while the pH is still less than 4.8, the bicarbonate concentration is still negligible. Therefore, the sodium bicarbonate addition rate can be controlled using the phase 1 control illustrated in FIG. **2**. However, the increased dilution water needed during sulfate release will result in a lower sorbent inlet conductivity (PCS) value, which is not indicative of the value needed for phase two control. Therefore, if sulfate release occurs, the pre-sorbent conductivity set-point used for phase two control should be based on the value, or profile, preceding the sulfate release. The sulfate release can be detected by monitoring changes in the dilution water rate and/or changes in the conductivity change across the sorbent cartridge. The sulfate release can be detected using the methods described above using the average plateau conductivity value and an increase relative to the average plateau value of 0.2-mS/cm. Values other than an increase of 0.2-mS/cm can be used depending on properties of the sorbent cartridge used or other factors such as dialysate prescription or patient parameters. The end of the sulfate release phase and the start of the second control phase can also be based on dilution water changes and/or sorbent cartridge conductivity changes, or can be based on a fixed volume, such as 5 or 10 liters of dialysate. In the case of using sorbent conductivity changes to determine the end of the sulfate release phase, the sorbent conductivity delta can continue to be monitored relative to the average plateau value and when it increases to a value of 0.44-mS/cm above the plateau value the sulfate release phase can be considered complete and the pH value above the phase 1 preset value. Any of the methods described for monitoring changes in sorbent cartridge effluent pH can also be used to determine if or when sulfate release occurs.

An example of the control approach utilized a prototype hemodialysis test system configured the same as FIG. **1**, with the addition of a pH sensor between the sorbent cartridge and degasser. A simulated patient 18-liter patient tank was connected to the dialyzer (Clearum HS13) and recirculated through inlet **103** and outlet **104** at a rate of 500-mL/min. The dialysate was recirculated at a flow rate of 600-mL/min through the dialyzer at inlet **106** and outlet **107**. The dialysate was controlled to a prescription composition target of 145-mM sodium, 40-mM bicarbonate, 2-mM potassium, 1.5-mM calcium and 0.375-mM magnesium. The patient had a composition of 131-mM sodium, 34.1-mM bicarbonate, 3.6-mM sulfate, 5-mM potassium, 0.4-mM magnesium, 1.3-mM calcium and 33-mM urea. The sorbent cartridge used contained activated carbon, urease, activated alumina, zirconium phosphate and hydrous zirconium oxide. A 200-minute simulated therapy was performed. FIG. **4** shows the sorbent outlet pH profile versus the cumulative dialysate volume during the simulated therapy. The pH stayed below 5 for the first 80-liters of dialysate and then increased to 6.5 by the end of therapy at 120-liters of dialysate. Also, shown in FIG. **4** is the delta conductivity across the sorbent cartridge calculated using equation 1. Finally, the sulfate level in the dialysate is shown over the course of therapy, where levels start to increase at 70-liters, peak at 97-liters and then start to decrease. For this simulated therapy, a plateau delta conductivity value of −2.59-mS/cm was calculated by averaging the delta conductivity from 60 to 65-liters. In order to determine when sulfate release occurred, and adjust the SCS conductivity target, a value of 0.2-mS/cm was used to compare to the plateau delta condo value. Using this value, the sulfate release was detected at 77-liters, which corresponds to a level of 1.5-mM sulfate as shown in FIG. 4. In order to determine when the pH exceeded a preset value of 4.9, and switch to phase 2 control, a value of 0.44 was used to compare to the plateau delta conductivity value. Using this value, a pH of 4.9 was predicted to occur at 88-liters, compared to the measured pH of 5.0 at 88-liters. The phase two control started at 88-liters and the bicarbonate metering rate (1000-mM solution of sodium bicarbonate shown as Q-Base in FIG. **1**) over the course of therapy is shown in FIG. **5**, along with the sorbent outlet pH profile. As shown in FIG. **5**, the bicarbonate pump rate steadily decreases after the start of phase 2 control due to the increasing sorbent outlet pH and the increase of bicarbonate at sorbent outlet, requiring less bicarbonate to be metered in to meet the prescription of 40-mM bicarbonate. The bicarbonate metering rate is relatively constant during the low pH phase from 0 to 88-liters. FIG. **6** shows the water pump metering rate (Q-H_2O in FIG. **1**) and sorbent outlet pH profile versus dialysate volume. As can be seen, as the pH starts to rise and the sulfate release starts to occur at 75-liters, the water metering starts to increase more rapidly. This increased water metering rate could also be used to predict when the sulfate release and preset pH value are reached. FIG. **7** shows the degasser pump output along with the sorbent outlet pH profile over the course of therapy. When the pH starts to rise above 4.9, the degasser output % decreases rapidly from about 50% to 40% when the pH increases from about 4.9 to 5.5. This change in degasser output could also be used to indicate when the preset pH value has been exceeded. FIG. **8** shows the measured dialysate sodium and bicarbonate levels along with the pH profile over the course of therapy. The target sodium level of 145-mM and the target bicarbonate (HCO3) level of 40-mM were achieved throughout therapy within 5% or better of target. Even during the rapid pH increase out of the sorbent cartridge starting at 85-liters, when the bicarbonate level leaving the sorbent cartridge starts to increase.

One of skill in the art will understand the data used in FIGS. **4-8** are from a simulated patient and provided for illustrative purposes only. The same methods can be used with any patient to accurately control the sodium and bicarbonate content of the dialysate.

One skilled in the art will understand that various combinations and/or modifications and variations can be made in the described systems and methods depending upon the specific needs for operation. Various aspects disclosed herein may be combined in different combinations than the combinations specifically presented in the description and accompanying drawings. Moreover, features illustrated or described as being part of an aspect of the disclosure may be used in the aspect of the disclosure, either alone or in combination, or follow a preferred arrangement of one or more of the described elements. Depending on the example, certain acts or events of any of the processes or methods described herein may be performed in a different sequence, may be added, merged, or left out altogether (e.g., certain described acts or events may not be necessary to carry out the techniques). In addition, while certain aspects of this disclosure are described as performed by a single module or unit for purposes of clarity, the techniques of this disclosure may be performed by a combination of units or modules associated with, for example, a medical device.

What is claimed is:

1. A system, comprising:

a dialysate flow path; the dialysate flow path fluidly connectable to a dialysate inlet of a dialyzer and a dialysate outlet of the dialyzer;

a sorbent cartridge in the dialysate flow path;

a degasser in the dialysate flow path downstream of the sorbent cartridge;

a bicarbonate source fluidly connected to the dialysate flow path;

a water source fluidly connected to the dialysate flow path;

a first conductivity sensor downstream of the sorbent cartridge; and

a control system; the control system programmed to determine a pH of a fluid exiting the sorbent cartridge; wherein:

while pH of the fluid exiting the sorbent cartridge is below a preset pH, the control system is programmed to control a sodium concentration in the fluid based on a sodium prescription and a conductivity measured by the first conductivity sensor; and to control a bicarbonate concentration in the fluid based on a bicarbonate prescription; and

while pH of the fluid exiting the sorbent cartridge is above a preset pH, the control system controls a sodium concentration in the fluid based on a sodium prescription and a conductivity measured by a second conductivity sensor upstream of the sorbent cartridge.

2. The system of claim **1**, wherein the preset pH is about 4.8.

3. The system of claim **1**, wherein the sorbent cartridge includes zirconium phosphate at a low pH.

4. The system of claim **1**, wherein while the pH of the fluid exiting the sorbent cartridge is below the preset pH, the control system is programmed to control the sodium concentration in the fluid by adding water from a water source upstream of the sorbent cartridge to a target post-sorbent conductivity setpoint.

5. The system of claim **1**, wherein while the pH of the fluid exiting the sorbent cartridge is below the preset pH, the control system is programmed to control the bicarbonate concentration in the fluid by adding bicarbonate from a bicarbonate source upstream of the sorbent cartridge to a target post-bicarbonate conductivity setpoint.

6. The system of claim **1**, further comprising a hydrochloric acid source fluidly connected to the dialysate flow path upstream of the sorbent cartridge.

7. The system of claim **1**, further comprising at least one infusate source downstream of the sorbent cartridge.

8. The system of claim **1**, wherein the control system is programmed to detect release of sulfate ions from the sorbent cartridge.

9. The system of claim **8**, wherein the control system is programmed to dilute the fluid during the release of sulfate ions.

10. The system of claim **1**, wherein while the pH of the fluid exiting the sorbent cartridge is above the preset pH, the control system is programmed to control the sodium concentration in the fluid by adding water from a water source upstream of the sorbent cartridge to a target pre-sorbent conductivity setpoint.

11. The system of claim **10**, wherein the target pre-sorbent conductivity setpoint is a conductivity measured upstream of the sorbent cartridge while the pH is below the preset pH.

12. The system of claim **10**, wherein while the pH of the fluid exiting the sorbent cartridge is above the preset pH, the control system is programmed to control the bicarbonate concentration in the fluid by adding bicarbonate to reach a target post-bicarbonate conductivity setpoint.

13. The system of claim **12**, wherein the target post-bicarbonate conductivity setpoint is based on the sodium and a bicarbonate prescription.

14. The system of claim **1**, wherein the pH of the fluid exiting the sorbent cartridge is measured with a pH sensor downstream of the sorbent cartridge.

15. The system of claim **1**, wherein the pH of the fluid exiting the sorbent cartridge is measured based on changes to a degasser output.

16. The system of claim **1**, wherein the pH of the fluid exiting the sorbent cartridge is measured based on a conductivity change across the sorbent cartridge measured by the first conductivity sensor and a second conductivity sensor upstream of the sorbent cartridge.

17. The system of claim **4**, wherein the pH of the fluid exiting the sorbent cartridge is measured based on a volume of the water added from the water source.

18. The system of claim **1**, the control system programmed to isolate the sorbent cartridge prior to determining the pH of the fluid exiting the sorbent cartridge.

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